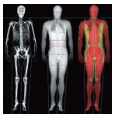


Certificate of Advanced Studies in Clinical Nutrition

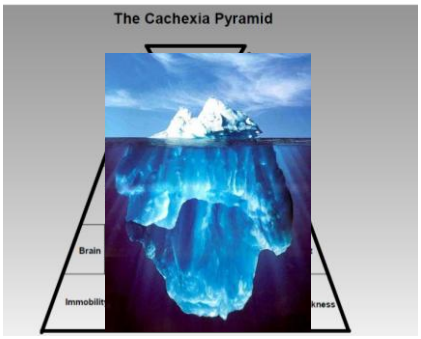
Cachexia : Update
How can nutritional assessment and support help to reduce chemotoxicity?

Dresse Jacquelin-Ravel Nathalie

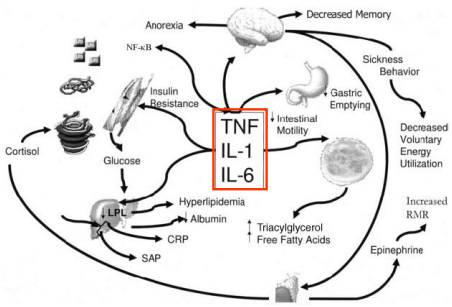
AIM

BSA / BMI / Lean Body Mass / Chemotoxicity

Cachexia definition : Consensus ?

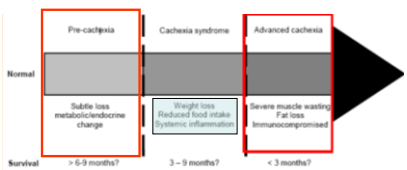


Cytokines



Am J Clin Nutr 2006;83:735- 43.

Classification of cachexia : a spectrum



Severe Muscle Wasting

Fearon K. Eur J Cancer 2008; 2008;44,1124-32

The term cachexia is currently in a process and reconceptualization and redefinition

« cachexia, is a complex metabolic syndrome associated with underlying disease illness and characterized by loss of muscle with or without loss of fat mass »
ESPEN

BMI and outcomes

original article

Annals of Oncology 19: 1613–1618, 2008
doi:10.1093/annonc/mdn168
Published online 23 April 2008

Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate

M. L. Telli[1], R. M. Witteles[2], G. A. Fisher[1] & S. Srinivas[1]*
[1]Division of Medical Oncology, Department of Medicine, [2]Division of Cardiovascular Medicine, Department of Medicine, Stanford University, Stanford, USA

Received 17 January 2008; revised 19 March 2008; accepted 20 March 2008

Background: In the pivotal phase III metastatic renal cell carcinoma trial, updated data indicates that 21% of sunitinib-treated patients experienced a decline in left ventricular ejection fraction to below normal. This cardiotoxicity was reported to be reversible and without clinical sequelae. We conducted a retrospective analysis of our institutional experience of cardiotoxicity with sunitinib after observing a high incidence of symptomatic heart failure.
Patients and methods: Patients receiving sunitinib at Stanford University from 1 July 2004 to 1 July 2007 were identified. Medical records were reviewed and those patients experiencing symptomatic grade 3/4 left ventricular systolic dysfunction were identified. Potential cardiac risk factors were analyzed.
Results: Forty-eight patients treated with sunitinib were assessable. Seven patients experienced symptomatic grade 3/4 left ventricular dysfunction 22–435 days after initiation of sunitinib. Three patients had persistent cardiac dysfunction after discontinuation of sunitinib and initiation of heart failure therapy. A history of congestive heart failure, coronary artery disease and lower body mass index were factors associated with increased risk.
Conclusions: Among patients treated with sunitinib at our institution, 15% developed symptomatic grade 3/4 heart failure. Future studies of sunitinib-related cardiotoxicity are urgently needed, particularly as the oncologic indications for this drug continue to expand.
Key words: cardiotoxicity, congestive heart failure, sunitinib, tyrosine kinase inhibitor

	CHF, $n = 7$	No CHF, $n = 41$	P
Mean age, years (SD)	67 (±9.1)	60 (±9.8)	0.09
Gender			
Male	4	35	0.11
Female	3	6	
Diagnosis			
Renal cell carcinoma	5	36	0.27
GIST	2	5	
Cardiac risk factors			
Hypertension	5	27	1.0
Preexisting	4	20	
On treatment	1	7	
Coronary artery disease	2	1	0.05
CHF/Cardiomyopathy	3	0	0.00
Diabetes mellitus	0	4	1.0
Hyperlipidemia	2	10	1.0
Mean body mass index	23.9	27.1	0.03
Normal (<25)	6	13	0.01
Overweight/obese (>25)	1	27	
Prior therapy			
Anthracycline	1[a]	0	0.14
Imatinib	2	5	0.27
Interferon	1	5	1.0
Sorafenib	0	8	0.58
Medications on sunitinib			
ACE inhibitor/ARB	4	14	0.40
Beta blocker	2	10	1.00
Sunitinib dosing schedule			
4 weeks on, 2 weeks off	6	33	1.0
Continuous daily dosing	1	8	

Impact of Body Mass Index on Outcomes and Treatment-Related Toxicity in Patients With Stage II and III Rectal Cancer: Findings From Intergroup Trial 0114

Jeffrey A. Meyerhardt, Joel E. Tepper, Donna Niedzwiecki, Donna R. Hollis, A. David McCollum, Denise Brady, Michael J. O'Connell, Robert J. Mayer, Bernard Cummings, Christopher Willett, John S. Macdonald, Al B. Benson III, and Charles S. Fuchs

A B S T R A C T

Purpose
To study the relationship between body mass index (BMI) and rates of sphincter-preserving operations, overall survival, cancer recurrence, and treatment-related toxicities in patients with rectal cancer.

Patients and Methods
We evaluated a nested cohort of 1,688 patients with stage II and III rectal cancer participating in a randomized trial of postoperative fluorouracil-based chemotherapy and radiation therapy.

Results
Obese patients were more likely to undergo an abdominoperineal resection (APR) than normal-weight patients (odds ratio, 1.77; 95% CI, 1.27 to 2.46). When analyzed by sex, increasing adiposity in men was a strong predictor of having an APR ($P < .0001$). Obese men with rectal cancer were also more likely than normal-weight men to have a local recurrence (hazard ratio [HR], 1.61; 95% CI, 1.00 to 2.59). In contrast, obesity was not predictive of cancer recurrence in women, nor was BMI predictive of overall mortality in either men or women. Underweight patients had an increased risk of death (HR, 1.43; 95% CI, 1.08 to 1.89) compared with normal-weight patients but no increase in cancer recurrences. Among all study participants, obese patients had a significantly lower rate of grade 3 to 4 leukopenia, neutropenia, and stomatitis and a lower rate of any grade 3 or worse toxicity when compared with normal-weight individuals.

Conclusion
Increasing BMI in male patients with rectal cancer is associated with a decreased likelihood of sphincter preservation and a higher chance of local recurrence. For both men and women, overweight and obese patients experience less toxicity associated with adjuvant chemoradiotherapy, suggesting that actual body weight dosing of fluorouracil for obese patients is justified.

J Clin Oncol 22:648-657. © 2004 by American Society of Clinical Oncology

BMI & Toxicity of 5 FU

Table 5. Major Treatment-Related Toxicity by Body Mass Index (% of patients)

	BMI Class					Unadjusted P Across All BMIs†	Adjusted P*	
	< 20 kg/m²	20-24.9 kg/m²	25-26.9 kg/m²	27-29.9 kg/m²	≥ 30 kg/m²		BMI ≥ 20 kg/m²‡	BMI < 26 kg/m²§
Nausea‖	5.5	5.1	3.9	5.2	3.0	.5	.3	1.0
Emesis¶	5.5	4.6	2.2	4.1	3.3	.4	.4	.8
Diarrhea#	22.1	26.0	25.6	29.8	22.5	.4	.4	.19
Leukopenia**	32.1	28.5	26.1	23.8	20.1	.04	.01	.8
Neutropenia††	43.1	45.5	43.6	34.6	26.1	.003	.0005	.17
Stomatitis‡‡	12.2	9.9	9.6	6.7	4.7	.03	.01	.7
Any grade 3 or 4 toxicity	81.7	75.7	79.9	71.7	70.0	.02	.05	.5

Among patients who were normal weight or heavier => **increasing BMI** was associated with a **significantly lower rate** of grade 3 and 4 leukopenia, neutropenia, stomatitis

Jeffrey A. J Clin Oncol : 2004 . 22:648-57

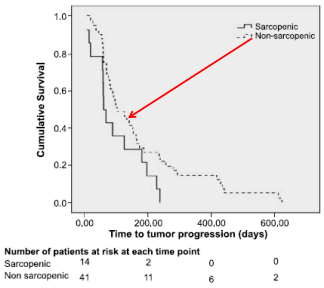
Muscle mass and outcomes ?

Sarcopenic Obesity: The Confluence of Two Epidemics

Ronenn Roubenoff

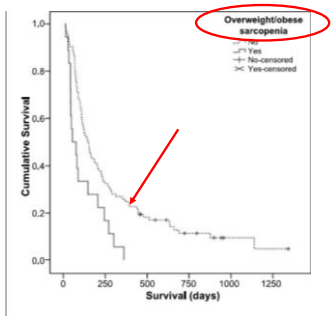
BMI, Lean Body Mass, the confluence of two parameters which emerging as important in relation to outcomes of cancer ?

Sarcopenic = ↓ Survival in metastatic Breast cancer



Prado MM. Clin Cancer Res ; 2009 : 2990-26

Survival & overweight/obese sarcopenia in pancreatic cancer



Prado MM. Clin Cancer Res ; 2009 : 2990-26

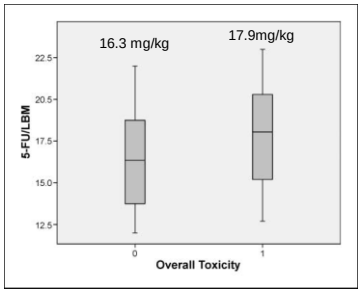
Sarcopenia as a Determinant of Chemotherapy Toxicity and Time to Tumor Progression in Metastatic Breast Cancer Patients Receiving Capecitabine Treatment

	Sarcopenic (n = 14; 25.5%)	Nonsarcopenic (n = 41; 74.5%)	P
Toxicity			
Present	7 (50.0%)	8 (20%)	0.03
Absent	7 (50.0%)	33 (80%)	
ECOG performance status*			
No performance impairment (scores 0-1)	9 (64%)	25 (65%)	1.00
Performance impairment (scores 2-3)	5 (36%)	14 (35%)	
Estrogen receptor status			
Positive	8 (57%)	31 (76%)	0.31
Negative	6 (43%)	10 (24%)	
HER-2 status			
Positive	3 (21%)	15 (37%)	0.35
Negative	11 (79%)	26 (63%)	
Characteristics mean (SD)			
Age	56.6 (11.4)	54.1 (10.1)	0.43
Weight (kg)	65.6 (11.4)	71.4 (16.7)	0.23
Height (m)	1.6 (0.1)	1.6 (0.1)	0.11
BMI (kg/m^2)	24.6 (4.0)	27.8 (5.7)	0.06
BSA (m^2)	1.7 (0.1)	1.8 (0.2)	0.42
Albumin †	39.8 (4.9)	39.1 (4.5)	0.60
Lumbar skeletal muscle index (cm^2/m^2)	35.0 (3.3)	47.4 (5.0)	<0.0001
Whole body lean mass (kg)	34.0 (3.3)	42.5 (5.0)	<0.0001
Mg capecitabine/kg LBM	104.2 (16.1)	86.9 (13.7)	<0.0001
Toxicity prevalence ‡			
Hand-foot syndrome	3 (21%)	4 (8%)	0.35
Diarrhea	4 (29%)	1 (2.4)	0.01
Stomatitis	5 (36%)	2 (4.9%)	0.008
Nausea	3 (21%)	3 (7%)	0.17
Vomit	1 (7%)	1 (2.4)	0.45
Neutropenia	1 (7.1%)	0	0.25

Same BSA
Lower lumber skeletal muscle
Higher dose/kg LBM

Carla M.M.Prado. Clin Cancer Res 2009;15:2920-2926

Body Composition as an Independent Determinant of 5-Fluorouracil – Based Chemotherapy Toxicity

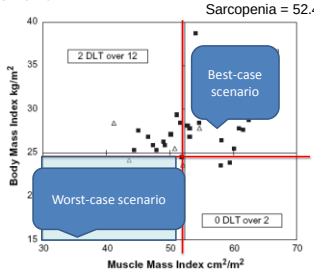


Planed dose of 5-FU = 425mg/m^2

Prado C. Clin Cancer Res 2007 ; 13 : 3264-68

Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma

Sarcopenia = 52.4cm2/m2



S.Antoun Annals Of Oncology 2010;21:1594-8

In this study :

- 7% of patients would be considered clinically underweight by accepted criteria (BMI<18.5Kg/m2)
- 67.6% of men and 50.1% of women are overweight or obese
- 54% are sarcopenic

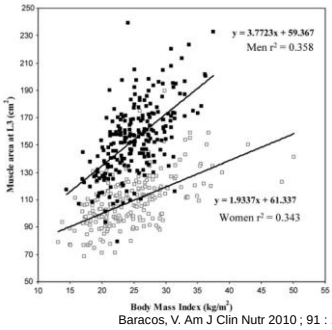
Body composition in patients with non–small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis[1–4]

Vickie E Baracos, Tony Reiman, Marina Mourtzakis, Ioannis Gioulbasanis, and Sami Antoun

Baracos, V. Am J Clin Nutr 2010 ; 91 : 1133S- 7S

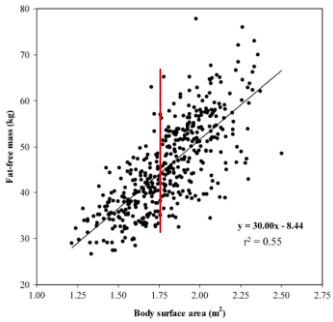
Variability in muscle area & BMI :

25.0 < BMI < 25.9 ; 114 cm² < muscle area L3 < 205 cm² ; 37.4 cm2 /m2 < skeletal muscle index < 72.4 cm2/m2



Baracos, V. Am J Clin Nutr 2010 ; 91 : 1133S- 7S

Fat-free mass not strongly related to BSA



Baracos, V. Am J Clin Nutr 2010 ; 91 : 1133S- 7S

Body surface area as a determinant of pharmacokinetics and drug dosing

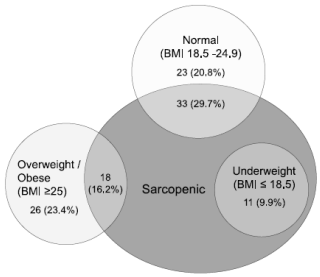
Michael Sawyer and Mark J. Ratain

Committee on Clinical Pharmacology, Department of Medicine, and Cancer Research Center, The University of Chicago, Chicago, IL, USA

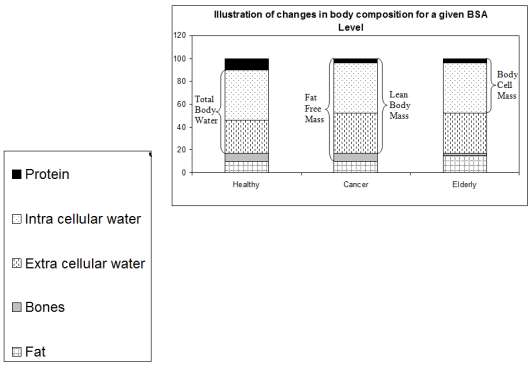
Conclusion

BSA was introduced in medical oncology to safely predict a suitable starting dose in phase I clinical trials from preclinical animal toxicology data. From that starting point in phase I trials it has spread throughout the practice of oncology with little justification. The formula to calculate body surface area takes two precisely quantifiable variables, height and weight, and estimates a value for surface area. The formula used to do this has never been adequately validated. Very few of the organ functions that determine the pharmacokinetics of a drug are related to body surface area; further when organ function has been related to body surface area other measures such as lean body weight have been found superior to surface area. For

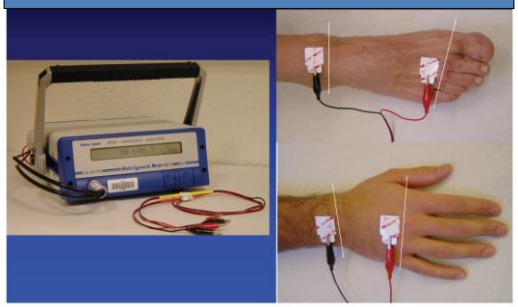
Invest New Drugs. 2001;19:171-7



Tan BHL. Clin Cancer Res ; 2009 : 6973-79



BIA Bioimpedance Analysis



Bioelectrical impedance phase angle as a prognostic indicator in advanced pancreatic cancer

Digant Gupta*, Christopher G. Lis, Sadie L. Dahlk, Pankaj G. Vashi, James F. Grutsch and Carolyn A. Lammersfeld

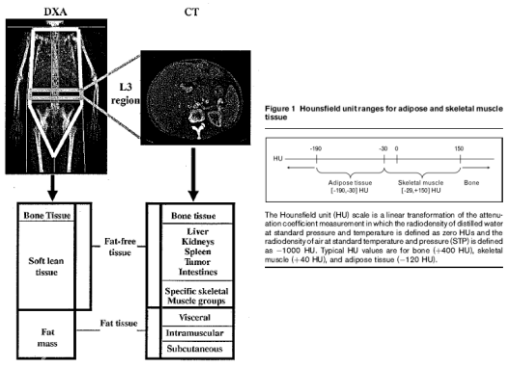
Cancer Treatment Centers of America® (CTCA) at Midwestern Regional Medical Center, 2520 Elisha Avenue, Zion, IL 60099, USA

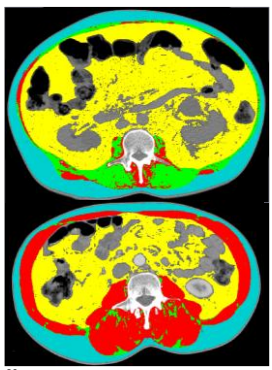
Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced colorectal cancer[1–3]

Digant Gupta, Carolyn A Lammersfeld, Jessica L Burrows, Sadie L Dahlk, Pankaj G Vashi, James F Grutsch, Sara Hoffman, and Christopher G Lis

Bioelectrical impedance phase angle as a prognostic indicator in breast cancer

Digant Gupta, Carolyn A Lammersfeld, Pankaj G Vashi, Jessica King, Sadie L Dahlk, James F Grutsch and Christopher G Lis*





SM = 31.66 cm2
AT = 575.5 cm2

BMI = 24.4 kg/m2

SM = 177.0 cm2
AT= 303.1 cm2

Cut Off
55.4cm2/m2
38.9cm2/m2

30

Nutri mful?

AGA Technical Review on Parenteral Nutrition

This literature review and the recommendations therein were prepared for the American Gastroenterological Association Clinical Practice and Practice Economics Committee. The paper was approved by the Committee on September 13, 2001, and by the AGA Governing Board on May 18, 2001.

Table 5. Meta-Analysis of Oncologic Trials

Outcome	Absolute risk difference[a]	Confidence intervals	Number of studies (patients) included
Mortality[b]	0%	−5%, +5%	19 (1050)
Total complication rate	+40%	+14%, +66%	8 (333)
Infectious complication rate	+16%	+8%, +23%	18 (823)
Tumor response	−7%[c]	−12%, −1%	15[d] (910)
Bone marrow toxicity	+22%	−10%, +54%	3 (134)
Gastrointestinal toxicity	+1%	−9%, +11%	6 (310)

[a]This represents the difference between the outcome in the treated group and the control group; a negative number represents a benefit for the treated group.
[b]Although 1 bone marrow transplantation trial reported an improved survival,[94] this was not demonstrated when all 4 trials[91–95] were combined; absolute risk difference equaled −5% (−14%, +5%). Only 3 of these trials provided parenteral nutrition during the time when the transplantation was performed[92–95]; when only these 3 trials were combined, absolute risk difference equaled −9% (−22%, +4%).
[c]A negative absolute risk difference indicates that the response rate in the control group was higher than in the recipients of the parenteral nutrition.
[d]13 of these 15 RCTs were chemotherapy trials.

Gastroenterology 2001;121:970-1101

Summary and implications of the data. Parenteral nutrition does not alter survival in patients receiving radiation or chemotherapy. The data cannot exclude the possibility that in-hospital parenteral nutrition will favorably affect survival in patients undergoing bone marrow transplantation.

In all other aspects, the use of parenteral nutrition in cancer patients receiving chemotherapy, radiation therapy, or bone marrow transplantation was clearly associated with net harm. Parenteral nutrition was associated with increases in total and infectious complication rates. In addition, parenteral nutrition was associated with an impaired tumor response to chemotherapy, which may be related to exogenous nutrients stimulating tumor growth.[14,143–146]

Gastroenterology 2001;121:970-1101

68. Popp MB, Fisher RI, Wesley R, Aamodt R, Brennan MF. A prospective randomized study of adjuvant parenteral nutrition in the treatment of advanced diffuse lymphoma: influence on survival. Surgery 1981;90:195–203.
69. Popp MB, Fisher RI, Simon RM, Brennan MF. A prospective randomized study of adjuvant parenteral nutrition in the treatment of diffuse lymphoma: effect on drug tolerance. Cancer Treat Rep 1981;65(Suppl 5):129–135.
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72. Serrou B, Cupissol D, Plagne R, Boutin P, Chollet P, Carcassone Y, Michel FB. Follow-up of a randomized trial for oat cell carcinoma evaluating the efficacy of peripheral intravenous nutrition (PIVN) as adjunct treatment. Recent Results Cancer Res 1982;80:246–253.
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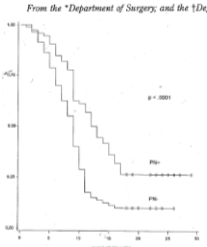
75. Shamberger RC, Brennan MF, Goodgame JT, Lowry SF, Maher MM, Wesley RA, Pizzo PA. A prospective, randomized study of adjuvant parenteral nutrition in the treatment of sarcomas: results of metabolic and survival studies. Surgery 1984;96:1–

Original Communications

The Influence of Early Supplementation of Parenteral Nutrition on Quality of Life and Body Composition in Patients With Advanced Cancer

Edward Shang, MD*; Christel Weiss, PhD†; Stefan Post, MD*; and Georg Kaehler, MD*

*From the *Department of Surgery, and the †Department of Biostatistics, University Hospital Mannheim, Mannheim, Germany*



Mediane survival rates : 12.5 months for PN +,
Vs 9 months for PN -

Schang E. JPEN 2006 ; 30 : 222-30

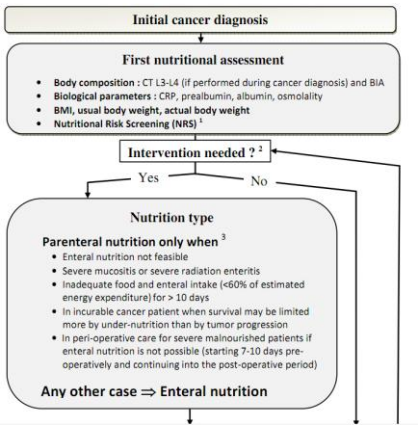
Does nutrition support cause cancer progression?

- Differences between experimental and human studies:
  - The ratio tumor/host exceeds 20% in animals while in human is < 1 – 2%
  - Tumor doubling time ranges from 2 to 7 days in animals while in human is one or more months
  - The difference in the duration of the tumor life relative time under TPN
  - Tumor immunogenicity

Guidelines ESPEN 2009

Indications	Therapeutic goals for PN in cancer patients are the improvement of function and outcome by: • preventing and treating under-nutrition/cachexia, • enhancing compliance with anti-tumor treatments, • controlling some adverse effects of anti-tumor therapies, • improving quality of life	C
	PN is ineffective and probably harmful in non-aphagic oncological patients in whom there is no gastrointestinal reason for intestinal failure	A
	PN is recommended in patients with severe mucositis or severe radiation enteritis	C
Nutritional provision	Supplemental PN is recommended in patients if inadequate food and enteral intake (<60% of estimated energy expenditure) is anticipated for more than 10 days	C
	PN is not recommended if oral/enteral nutrient intake is adequate	A
	In the presence of systemic inflammation it appears to be extremely difficult to achieve whole body protein anabolism in cancer patients. In this situation, in addition to nutritional interventions, pharmacological efforts are recommended to modulate the inflammatory response	C
	Preliminary data suggest a potential positive role of insulin (Grade C). There are no data on n-3 fatty acids	C
Peri-operative care	Peri-operative PN is recommended in malnourished candidates for artificial nutrition, when EN is not possible	A
	Peri-operative PN should not be used in the well-nourished	A
During non-surgical therapy	The routine use of PN during chemotherapy, radiotherapy or combined therapy is not recommended	A
	If patients are malnourished or facing a period longer than one week of starvation and enteral nutritional support is not feasible, PN is recommended	C
Incurable patients	In intestinal failure, long-term PN should be offered, if (1) enteral nutrition is insufficient, (2) expected survival due to tumor progression is longer than 2–3 months,[1,3] it is expected that PN can stabilize or improve performance status and quality of life, and [4] the patient desires this mode of nutritional support	C
	There is probable benefit in supporting incurable cancer patients with weight loss and reduced nutrient intake with "supplemental" PN	B

Take home message



Follow-up

- **Every week :** NRS assessment
- **Every 3 weeks :**
  Body composition = BIA + CT L3-L4 (if performed for tumor response)
  Biological parameters

[1] Nutritional Risk Screening

[2] Nutritional intervention criteria (any of the following items)

- NRS ≥ 3
- Albumin < 30 g/l
- Loss > 10% of the usual body weight in 6 months or 5% in 1 month
- Nutritional intake less than 60% of estimated energy expenditure
- Worsening of fat mass and/or fat free mass (CT/BIA) *independent of BMI*
- Undergoing major neck and abdominal surgery (*independent of the nutritional risk*)
- With obvious undernutrition at the time of surgery

[3] ESPEN Guidelines http://www.espen.org/documents/0909/Non-surgical%20oncology.pdf

Thank you for your attention !
Jacquelin-Ravel.N
IMO, Genolier, Switzerland